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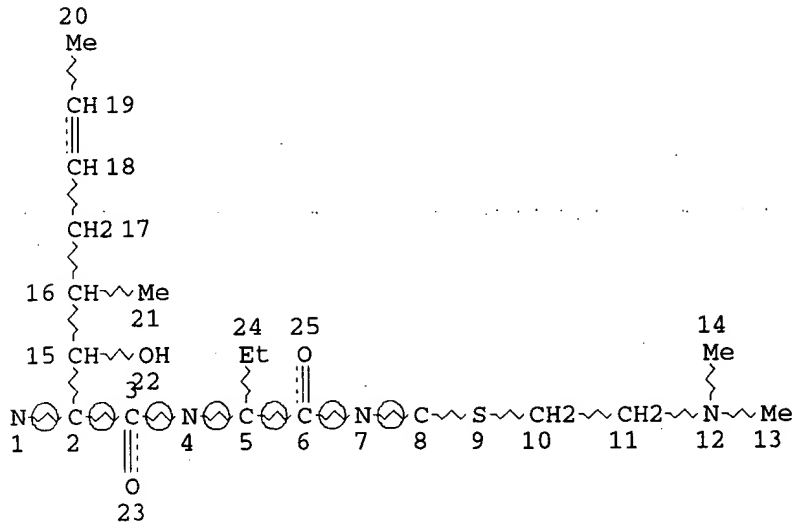

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  25

STEREO ATTRIBUTES: NONE
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L8             7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7

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L8   ANSWER 1 OF 7  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:47768  HCAPLUS
DOCUMENT NUMBER:          140:263758
TITLE:                    Substitution in Position 3 of Cyclosporin A Abolishes
                          the Cyclophilin-mediated Gain-of-function Mechanism
                          but Not Immunosuppression
AUTHOR(S):                Baumgrass, Ria; Zhang, Yixin; Erdmann, Frank; Thiel,
                          Andreas; Weiwad, Matthias; Radbruch, Andreas; Fischer,
                          Gunter
CORPORATE SOURCE:         Max Planck Research Unit for Enzymology of Protein
                          Folding, Halle-Saale, D-06120, Germany
SOURCE:                   Journal of Biological Chemistry (2004), 279(4),
                          2470-2479
                          CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER:                American Society for Biochemistry and Molecular
                          Biology
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
```

AB Binary complex formation between the immunosuppressive drug cyclosporin A (CsA) and cyclophilin 18 is the prerequisite for the ability of CsA to inhibit the protein phosphatase activity of calcineurin, a central mediator of antigen-receptor signaling. We show here that several CsA derivs. substituted in position 3 can inhibit calcineurin without prior formation of a complex with cyclophilin 18. [Methylsarcosine3]CsA was shown to inhibit calcineurin, either in its free form with an IC50 value of 10 μM, or in its complex form with cyclophilin 18 with an IC50 of 500 nM. [Dimethylaminoethylthiosarcosine3]CsA ([Dat-Sar3]CsA) was found to inhibit calcineurin on its own, with an IC50 value of 1.0 μM, but was not able to inhibit calcineurin after forming the [Dat-Sar3]CsA-cyclophilin 18 binary complex. Despite their different inhibitory properties, both CsA and [Dat-Sar3]CsA suppressed T cell proliferation and cytokine production mainly through blocking NFAT activation and interleukin-2 gene expression. Furthermore, to demonstrate that [Dat-Sar3]CsA can inhibit calcineurin in a cyclophilin-independent manner in vivo, we tested its effect in a Saccharomyces cerevisiae strain (Δ12), in which all the 12 cyclophilins and FKBPs were deleted. [Dat-Sar3]CsA, but not CsA, bypassed the requirement for cellular cyclophilins and caused growth inhibition in the salt-stressed Δ12 strain.

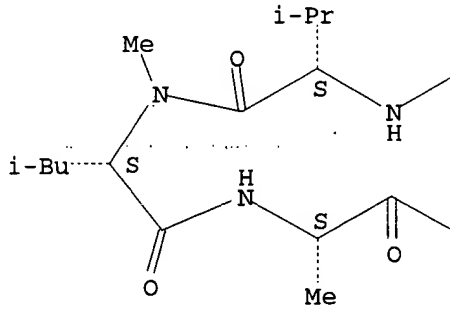
IT **210760-77-3**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(substitution in position 3 of cyclosporin A abolishes the cyclophilin-mediated gain-of-function mechanism but not immunosuppression)

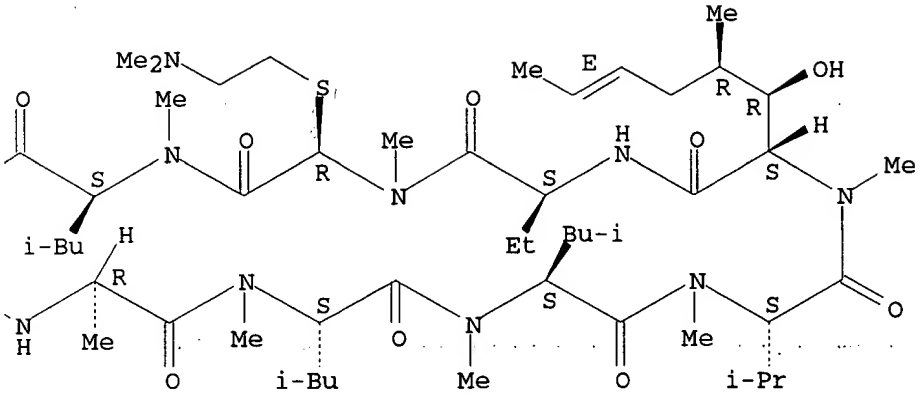
RN 210760-77-3 HCAPLUS

CN Cyclosporin A, 8-[(2R)-2-[[2-(dimethylamino)ethyl]thio]-N-methylglycine]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A





REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

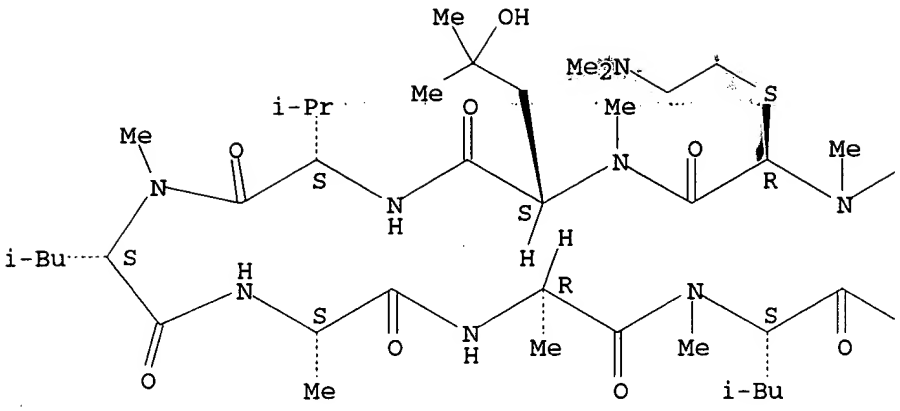
L8 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:928882 HCAPLUS
DOCUMENT NUMBER: 140:146494
TITLE: Synthesis of non-immunosuppressive cyclophilin-Binding cyclosporin A derivatives as potential anti-HIV-1 drugs
AUTHOR(S): Evers, Michel; Barriere, Jean-Claude; Bashiardes, Georges; Bousseau, Anne; Carry, Jean-Christophe; Dereu, Norbert; Filoche, Bruno; Henin, Yvette; Sable, Serge; Vuilhorgne, Marc; Mignani, Serge
CORPORATE SOURCE: Aventis Pharma S.A., Centre de Recherche de Paris, Vitry-sur-Seine, 94403, Fr.
SOURCE: Bioorganic & Medicinal Chemistry Letters (2003), 13(24), 4415-4419
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:146494

AB Original cyclosporin A (CsA) derivs. bearing various alkylthio side chains at the sarcosine residue 3 (R configuration) and for the most potent and selective compds. a 4'-hydroxyl group at the Me-Leucine residue 4 were prepared in one or two steps from com. available CsA. The [2-(di-Me or diethylamino)-ethylthio-Sar]3-[(4'-OH)MeLeu]4-CsA derivs. displayed potent in vitro anti-HIV-1 (IC50 .apprx.46 nM) and low immunosuppressive activities (IC50≥1500 nM).

IT **210759-10-7P**
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of non-immunosuppressive cyclophilin-Binding cyclosporin A derivs. as potential anti-HIV-1 drugs)
RN 210759-10-7 HCAPLUS
CN Cyclosporin A, 8-[(2R)-2-[[2-(dimethylamino)ethyl]thio]-N-methylglycine]-9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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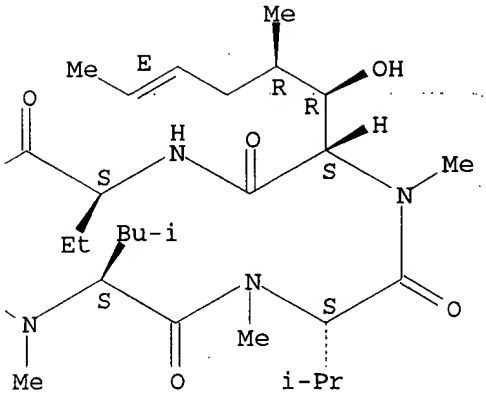
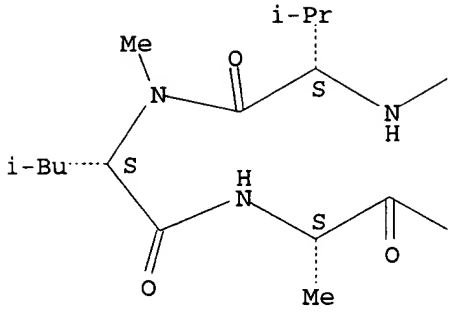


IT **210760-77-3P**
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of non-immunosuppressive cyclophilin-Binding cyclosporin A derivs. as potential anti-HIV-1 drugs)
RN 210760-77-3 HCAPLUS
CN Cyclosporin A, 8-[(2R)-2-[[2-(dimethylamino)ethyl]thio]-N-methylglycine]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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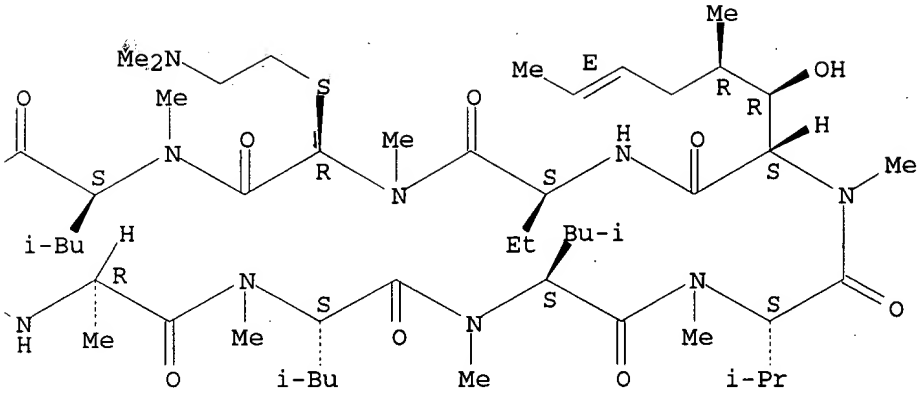


REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:819403 HCAPLUS
DOCUMENT NUMBER: 132:36039
TITLE: Preparation of cyclosporin derivatives via deprotonation reaction
INVENTOR(S): Viskov, Christian
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer SA, Fr.
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9967280	A1	19991229	WO 1999-FR1480	19990621

W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU,

ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX,
NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU,
ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

FR 2780061	A1	19991224	FR 1998-7846	19980622
FR 2780061	B1	20010907		
AU 9942700	A1	20000110	AU 1999-42700	19990621
EP 1098903	A1	20010516	EP 1999-957167	19990621
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2002518519	T2	20020625	JP 2000-555931	19990621
US 2001025025	A1	20010927	US 2000-742008	20001222

PRIORITY APPLN. INFO.: FR 1998-7846 A 19980622
WO 1999-FR1480 W 19990621

OTHER SOURCE(S): CASREACT 132:36039; MARPAT 132:36039

AB The invention concerns a novel method for preparing an intermediate polyanion for preparing cyclosporin derivs. by treating a cyclosporin with a hexamethyldisilazane metal salt, optionally in the presence of a metal halide. The treated cyclosporin has one or several free hydroxy groups and/or non-methylated nitrogen atoms in position α and/or any other acid group capable of deprotonation which are optionally deprotonated or in protected form. Thus, [(R)-2-(N,N-dimethylamino)ethylthio-Sar]3 cyclosporine A was prepared in 53 % yield via coupling of cyclosporine A with di-[2-(N,N-dimethylamino)ethyl] disulfide in presence of hexamethyldisilazane lithium salt and cesium chloride in tert-butylmethyl ether and toluene.

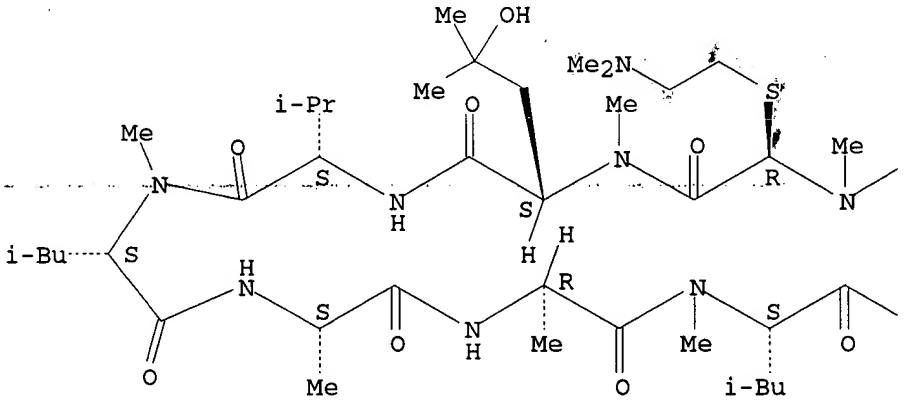
IT **210759-10-7P 227937-27-1P**
RL: BPN (Biosynthetic preparation); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of cyclosporin derivs. via coupling and deprotonation reactions)

RN 210759-10-7 HCAPLUS

CN Cyclosporin A, 8-[(2R)-2-[[2-(dimethylamino)ethyl]thio]-N-methylglycine]-9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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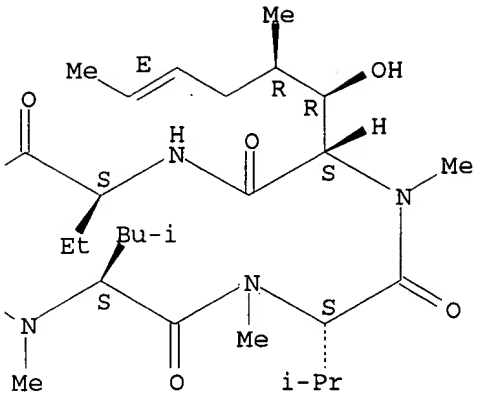


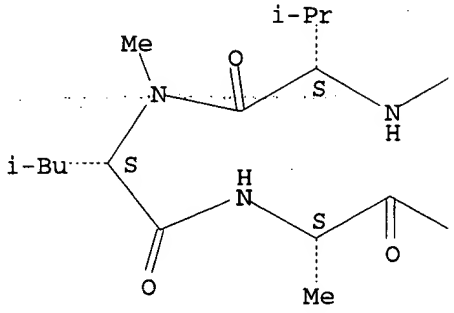
RN 227937-27-1 HCAPLUS
CN Cyclosporin A, 8-[(2R)-2-[[2-(dimethylamino)ethyl]thio]-N-methylglycine]-, monomethanesulfonate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 210760-77-3
CMF C66 H120 N12 O12 S

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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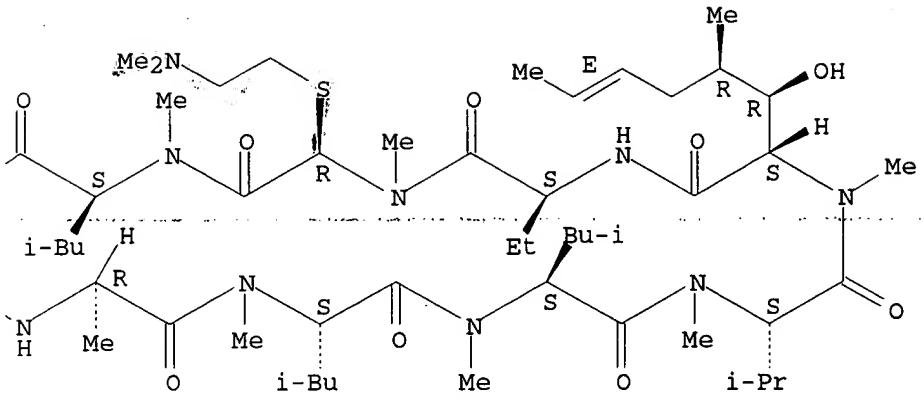
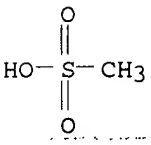


CM 2

CRN 75-75-2
CMF C H4 O3 S



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L8 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:811267 HCAPLUS
DOCUMENT NUMBER: 132:50254
TITLE: Preparation of novel cyclosporins
INVENTOR(S): Ellmerer-Mueller, Ernst; Brossner, Dagmar; Maslouh, Najib; Ambrosi, Horst-Dieter; Jas, Gerhard
PATENT ASSIGNEE(S): C-Chem A.-G., Switz.
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9965933	A1	19991223	WO 1999-EP4012	19990610

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,

CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2334730	AA	19991223	CA 1999-2334730	19990610
AU 9948993	A1	20000105	AU 1999-48993	19990610
AU 760168	B2	20030508		
EP 1086124	A1	20010328	EP 1999-932697	19990610
EP 1086124	B1	20031119		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
BR 9911160	A	20010403	BR 1999-11160	19990610
JP 2002518406	T2	20020625	JP 2000-554758	19990610
AT 254630	E	20031215	AT 1999-932697	19990610
PT 1086124	T	20040430	PT 1999-932697	19990610
ES 2212583	T3	20040716	ES 1999-932697	19990610
NO 2000006282	A	20010212	NO 2000-6282	20001211
US 6583265	B1	20030624	US 2001-701542	20010108

PRIORITY APPLN. INFO.: EP 1998-110761 A 19980612
WO 1999-EP4012 W 19990610

OTHER SOURCE(S): MARPAT 132:50254
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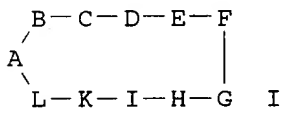


AB Compds. I [A = L-α-N-methylamino-β-hydroxy acid residue; B = α-aminobutyric acid, norvaline, threonine, or valine residue; C = substituted sarcosine residue; D = N-methyleucine, γ-hydroxy-N-methylleucine, N-methylvaline, or N-methylisoleucine residue; E = valine residue; F = N-methylleucine residue; G = alanine residue; H = Gly, D-alanine, D-serine, or O-hydroxyethyl-D-serine residue; I, K = N-methylleucine residue; L = N-methylvaline residue] were prepared Thus, 3-(pyridyl-2-thio)cyclosporin was prepared by treatment of cyclosporin A with 2,2'-dipyridyl disulfide and showed IC50 = 0.2 ng/mL for binding of cyclophilin.

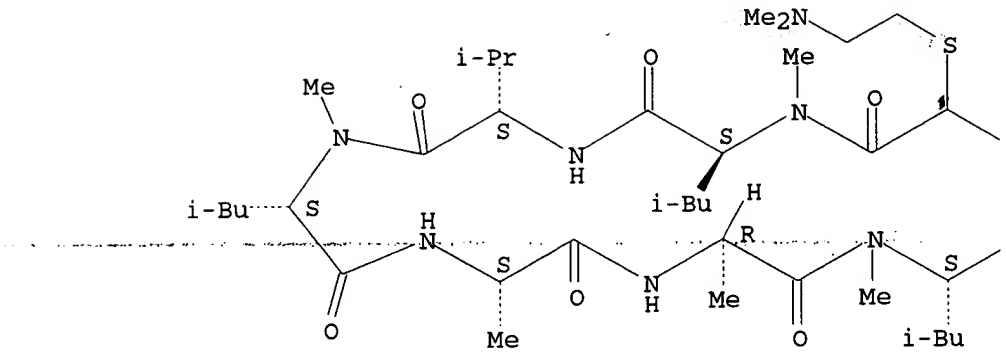
IT **252731-38-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of novel cyclosporins)

RN 252731-38-7 HCAPLUS

CN Cyclosporin A, 8-[2-[[2-(dimethylamino)ethyl]thio]-N-methylglycine]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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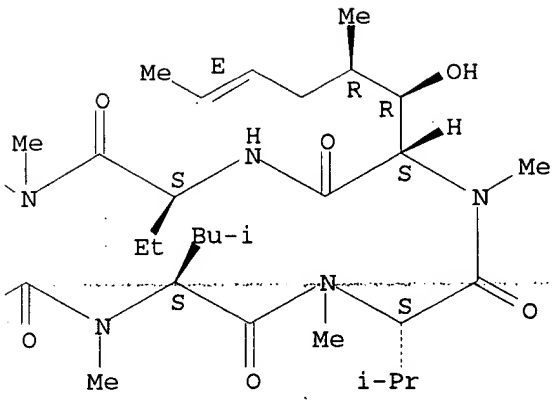

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:425790 HCAPLUS
DOCUMENT NUMBER: 131:59141
TITLE: Preparation of cyclosporins modified in position 3 via polyanions and coupling reaction
INVENTOR(S): Amouret, Guy; Guerreiro, Antonio; Viskov, Christian; Mignani, Serge; Evers, Michel; Barriere, Jean-Claude; Bashiardes, Georges; Carry, Jean-Christophe; Filoche, Bruno
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer S.A., Fr.
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9932512		A1	19990701	WO 1998-FR2745	19981216
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	RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
FR 2772768		A1	19990625	FR 1997-16189	19971219
FR 2772768		B1	20000114		
ZA 9811531		A	19990615	ZA 1998-11531	19981215
AU 9917640		A1	19990712	AU 1999-17640	19981216
EP 1040121		A1	20001004	EP 1998-962475	19981216
EP 1040121		B1	20040721		
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI			
JP 2002502803		T2	20020129	JP 2000-525449	19981216
AT 271563		E	20040815	AT 1998-962475	19981216
ES 2224454		T3	20050301	ES 1998-962475	19981216
PRIORITY APPLN. INFO.:				FR 1997-16189 A	19971219
				WO 1998-FR2745 W	19981216

OTHER SOURCE(S): CASREACT 131:59141; MARPAT 131:59141

AB The invention concerns a novel method for preparing a polyanion useful for preparing cyclosporin derivs. modified in position 3 by treating a cyclosporin with an alkali amide in liquid ammonia or in an aliphatic amine of low mol. weight, in the presence of a cosolvent, and optionally in the presence of dimethylpropyleneurea (DMPU). The treated cyclosporin has one or several free hydroxy groups and/or non-methylated nitrogen atoms in position α and/or any other acid group capable of being subjected to deprotonation and which are optionally subjected to deprotonation, or are in protected form. Thus, [(R)-2-(N-methyl-N-tert-butylamino)ethylthio-Sar]3-[4'-hydroxy-MeLeu]4-cyclosporin A was prepared via coupling of [4'-hydroxy-MeLeu]4-cyclosporin A with di-[2-(N,N-diethylamino)ethyl] disulfide in t-butylmethylether.

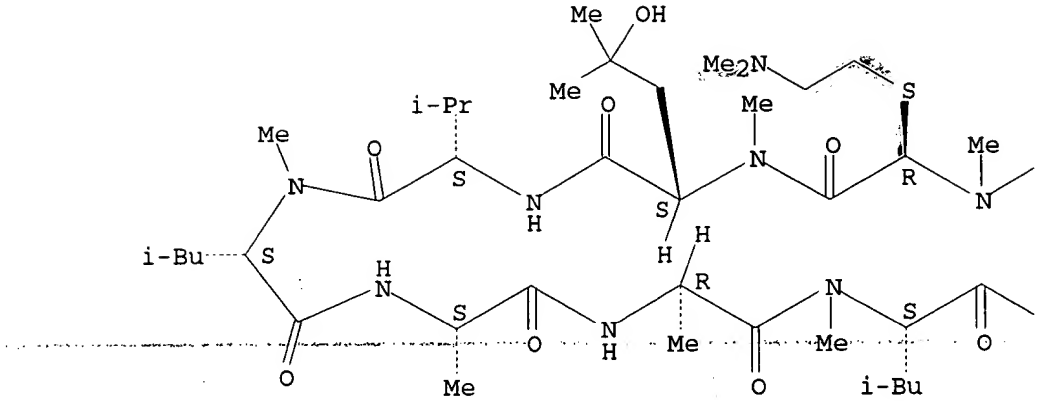
IT **210759-10-7P 227937-27-1P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of cyclosporins modified in position 3 via polyanions and coupling reaction)

RN 210759-10-7 HCAPLUS

CN Cyclosporin A, 8-[(2R)-2-[[2-(dimethylamino)ethyl]thio]-N-methylglycine]-9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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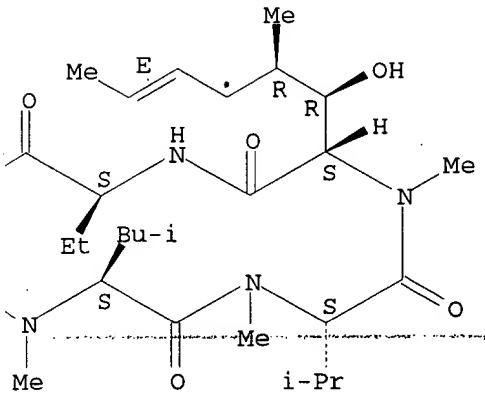


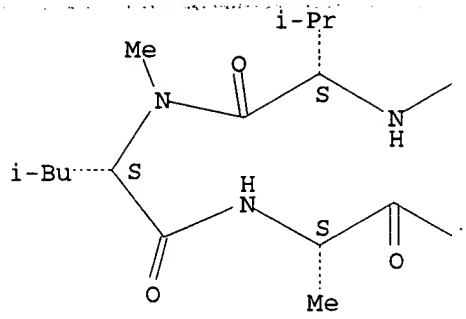
RN 227937-27-1 HCAPLUS
CN Cyclosporin A, 8-[(2R)-2-[[2-(dimethylamino)ethyl]thio]-N-methylglycine]-, monomethanesulfonate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 210760-77-3
CMF C66 H120 N12 O12 S

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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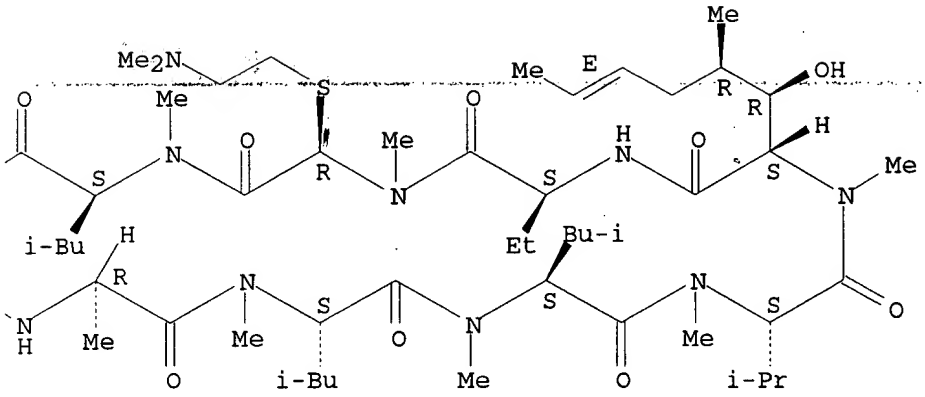

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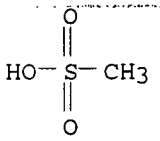
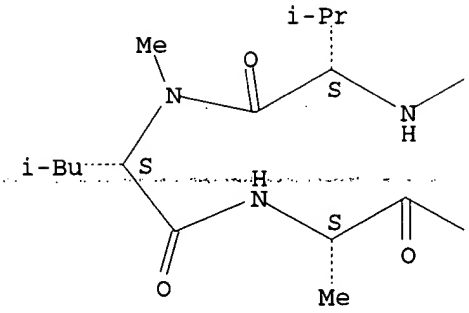


IT **210760-77-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cyclosporins modified in position 3 via polyanions and coupling reaction)
RN 210760-77-3 HCAPLUS
CN Cyclosporin A, 8-[(2R)-2-[[2-(dimethylamino)ethyl]thio]-N-methylglycine]-

(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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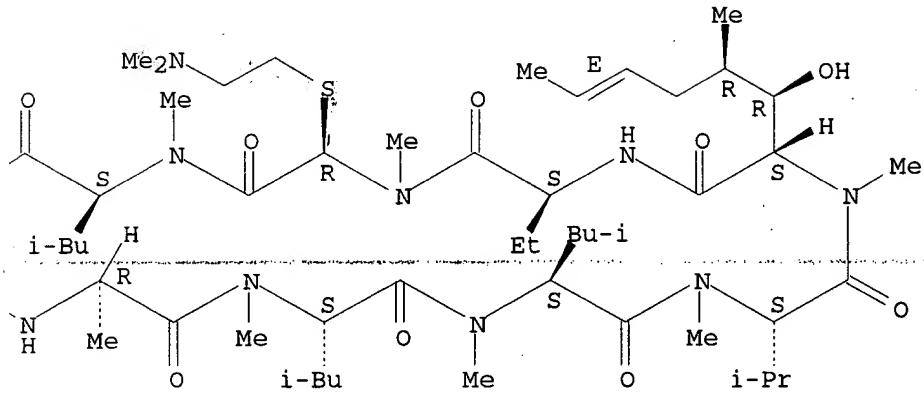

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:561743 HCAPLUS
DOCUMENT NUMBER: 129:149255
TITLE: Preparation of cyclosporin derivatives and their pharmaceutical compositions
INVENTOR(S): Barriere, Jean Claude; Carry, Jean Christophe; Filoche, Bruno; Evers, Michel; Bashiardes, Georges; Mignani, Serge; Leconte, Jean Pierre
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer SA, Fr.
SOURCE: Fr. Demande, 21 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2757522	A1	19980626	FR 1996-15956	19961224
FR 2757522	B1	19990129		
ZA 9711606	A	19980625	ZA 1997-11606	19971223
WO 9828329	A1	19980702	WO 1997-FR2405	19971223
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RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9856692	A1	19980717	AU 1998-56692	19971223
US 5965527	A	19991012	US 1997-996699	19971223
EP 948527	A1	19991013	EP 1997-952998	19971223
EP 948527	B1	20020605		
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JP 2001507346	T2	20010605	JP 1998-528489	19971223
AT 218580	E	20020615	AT 1997-952998	19971223
PT 948527	T	20021129	PT 1997-952998	19971223
ES 2178037	T3	20021216	ES 1997-952998	19971223
PRIORITY APPLN. INFO.:			FR 1996-15956 A	19961224
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OTHER SOURCE(S): MARPAT 129:149255
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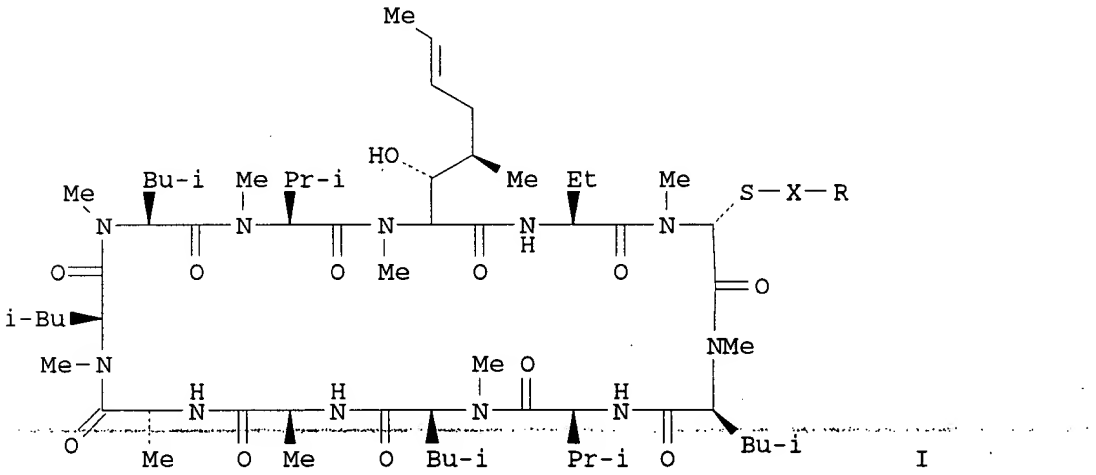


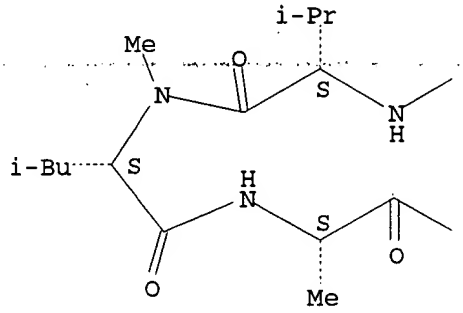
I

AB Cyclosporin derivs. I (X = alkylene or cycloalkylene; R = CO2H, carbalkoxy, NR1R2, where R1 and R2 are H, alkyl, cycloalkyl, substituted Ph, benzyl, heterocyclyl or R1R2N = heterocyclyl) were prepared for use in pharmaceutical compns. optionally associated with an antiviral, immunomodulator, or antimicrobial agent. Thus, treatment of cyclosporin A with bis[2-(diethylamino)ethyl] disulfide afforded I (X = ethylene, R = Et).

IT **210760-77-3P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of cyclosporin derivs. and their pharmaceutical compns.)
RN 210760-77-3 HCAPLUS
CN Cyclosporin A, 8-[(2R)-2-[[2-(dimethylamino)ethyl]thio]-N-methylglycine]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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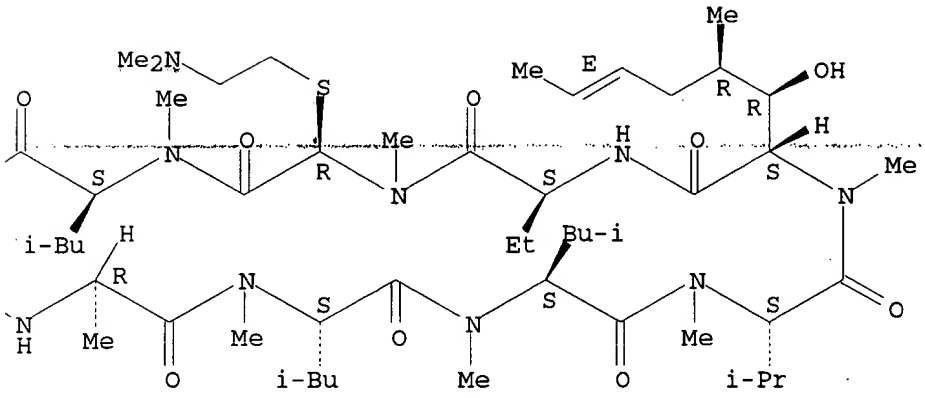

L8 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:561742 HCAPLUS
DOCUMENT NUMBER: 129:149254
TITLE: Preparation of cyclosporin derivatives and their pharmaceutical compositions
INVENTOR(S): Barriere, Jean Claude; Carry, Jean Christophe; Filoche, Bruno; Evers, Michel; Bashiardes, Georges; Mignani, Serge
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer SA, Fr.

SOURCE: Fr. Demande, 22 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2757521	A1	19980626	FR 1996-15955	19961224
FR 2757521	B1	19990129		
ZA 9711607	A	19980624	ZA 1997-11607	19971223
WO 9828330	A1	19980702	WO 1997-FR2406	19971223
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GH, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9856693	A1	19980717	AU 1998-56693	19971223
EP 951474	A1	19991027	EP 1997-952999	19971223
EP 951474	B1	20020605		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
US 5994299	A	19991130	US 1997-997612	19971223
JP 2001507347	T2	20010605	JP 1998-528490	19971223
AT 218582	E	20020615	AT 1997-952999	19971223
PT 951474	T	20021129	PT 1997-952999	19971223
ES 2178038	T3	20021216	ES 1997-952999	19971223

PRIORITY APPLN. INFO.: FR 1996-15955 A 19961224
WO 1997-FR2406 W 19971223

OTHER SOURCE(S): MARPAT 129:149254
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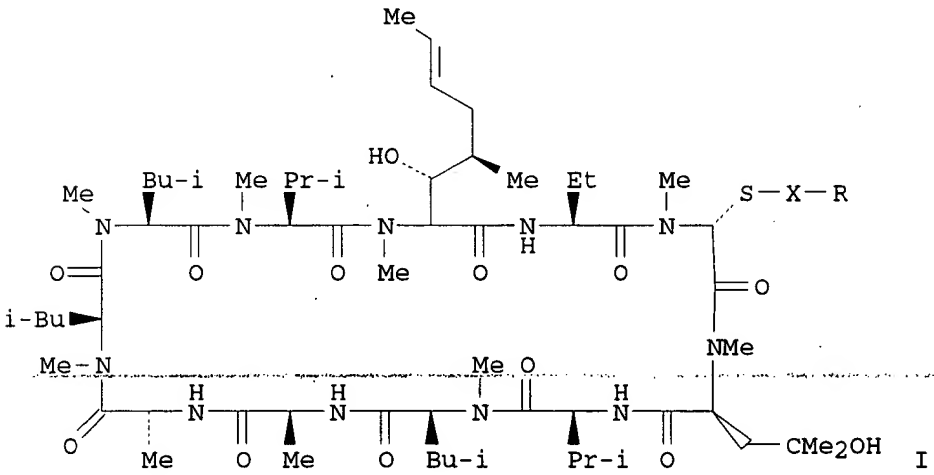


AB Cyclosporin derivs. I (X = alkylene or cycloalkylene; R = OH, CO2H, carbalkoxy, NR1R2, where R1 and R2 are H, alkyl, cycloalkyl, substituted Ph, benzyl, heterocyclyl or R1R2N = heterocyclyl) were prepared for use in

pharmaceutical compns. optionally associated with an antiviral, immunomodulator, or antimicrobial agent. Thus, treatment of 4'-hydroxy-4-MeLeu cyclosporin with bis[2-(dimethylamino)ethyl] disulfide afforded I (X = ethylene, R = Me).

IT **210759-10-7P**

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

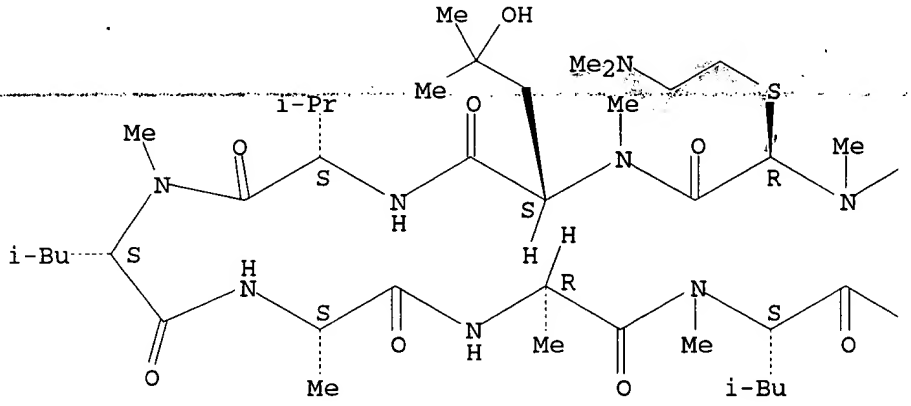
(preparation of cyclosporin derivs. and their pharmaceutical compns.)

RN 210759-10-7 HCAPLUS

CN Cyclosporin A, 8-[(2R)-2-[[2-(dimethylamino)ethyl]thio]-N-methylglycine]-9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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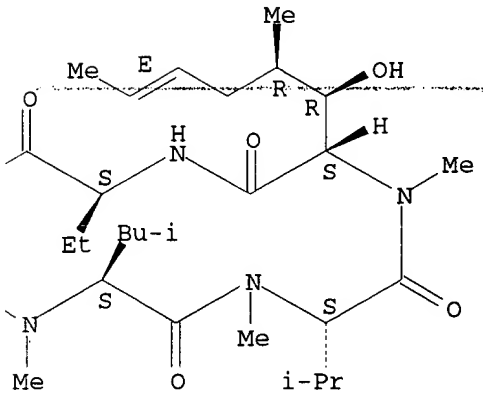

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COPYRIGHT (c) 2005 Beilstein-Institut zur Foerderung der Chemischen Wissenschaften
licensed to Beilstein GmbH and MDL Information Systems GmbH

FILE RELOADED ON OCTOBER 20, 2002
FILE LAST UPDATED ON APRIL 21, 2005

FILE COVERS 1771 TO 2004.
*** FILE CONTAINS  9,218,366 SUBSTANCES ***

>>>PLEASE NOTE: Reaction Data and substance data are stored in
   separate documents and can not be searched together in one query.
   Reaction data for BEILSTEIN compounds may be displayed
   immediately with the display codes PRE (preparations) and REA
   (reactions).  A substance answer set retrieved after the search
   for a chemical name, a compounds with available reaction
   information by combining with PRE/FA, REA/FA or more generally
   with RX/FA. The BEILSTEIN Registry Number (BRN) is the link
   between a BEILSTEIN compound and belonging reactions. For mo
   detailed reaction searches BRNs can be searched as reaction
   partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE  <<<

**********************************************************************
* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST.                 *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE    *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE           *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS.                         *
* FOR PRICE INFORMATION SEE HELP COST                                 *
**********************************************************************
   NEW
* PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE
  SEARCHED, SELECTED AND TRANSFERRED.
* NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES,
  ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A
  COMPOUND AT A GLANCE.

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L4              STR
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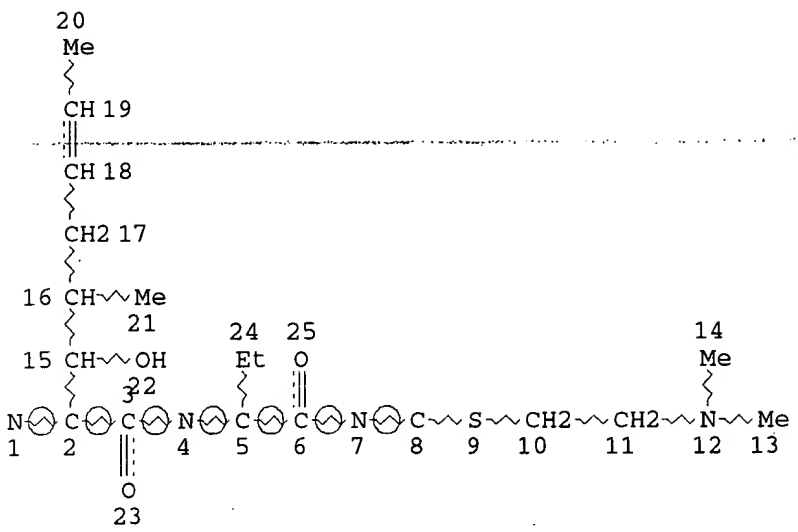

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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE
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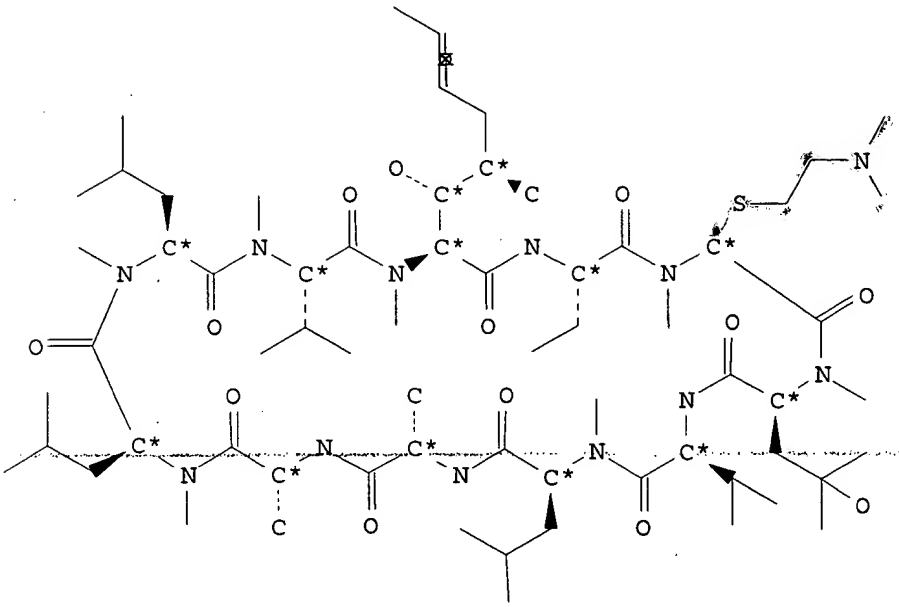
L10 ANSWER 1 OF 2 BEILSTEIN COPYRIGHT 2005 BEILSTEIN MDL on STN

Beilstein Records (BRN):	9609974
Molec. Formula (MF):	C66 H120 N12 O13 S
Molecular Weight (MW):	1321.81
Lawson Number (LN):	30810, 3125, 2817
File Segment (FS):	Stereo compound
Compound Type (CTYPE):	heterocyclic
Constitution ID (CONSID):	8102832
Tautomer ID (TAUTID):	9012535
Entry Date (DED):	2004/04/23
Update Date (DUPD):	2004/04/23



Field Availability:

Code	Name	Occurrence
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AUN	Autonomname	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	3
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
DED	Entry Date	1
DUPD	Update Date	1
MP	Melting Point	1
PHARM	Pharmacological Data	4

This substance also occurs in Reaction Documents:

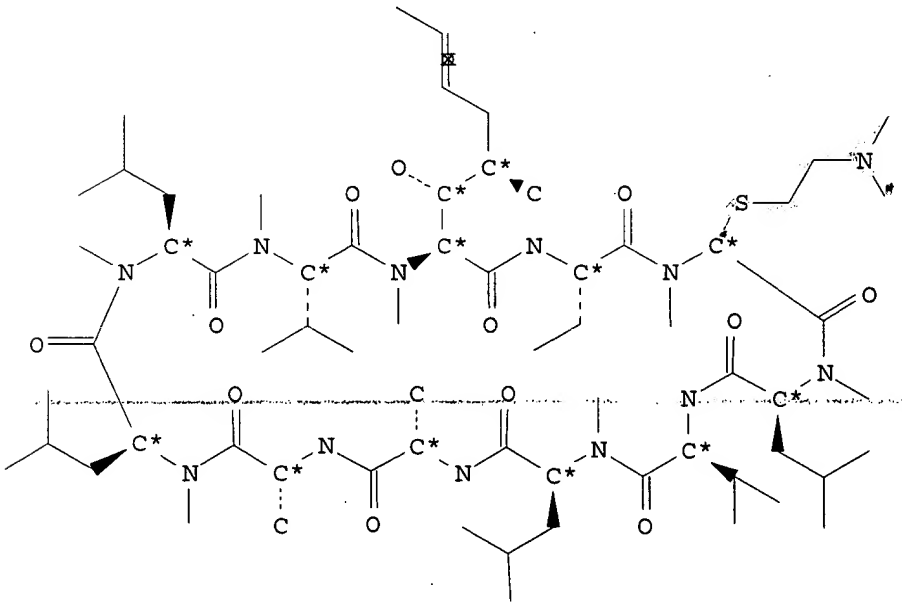
Code	Name	Occurrence
RX	Reaction Documents	1
RXPRO	Substance is Reaction Product	1

All References:
ALLREF

1. Evers, Michel; Barriere, Jean-Claude; Bashiardes, Georges; Bousseau, Anne; Carry, Jean-Christophe; Dereu, Norbert; Filoche, Bruno; Henin, Yvette; Sable, Serge; Vuilhorgne, Marc; Mignani, Serge, Bioorg.Med.Chem.Lett., CODEN: BMCLE8, 13(24), <2003>, 4415 - 4420; BABS-6424663

L10 ANSWER 2 OF 2 BEILSTEIN COPYRIGHT 2005 BEILSTEIN MDL on STN

Beilstein Records (BRN):	9609860
Chemical Name (CN):	27-(2-dimethylamino-ethylsulfanyl)-30-ethyl-33-(1-hydroxy-2-methyl-hex-4-enyl)-6,9,18,24-tetraisobutyl-3,21-diisopropyl-1,4,7,10,12,15,19,25,28-nonamethyl-1,4,7,10,13,16,19,22,25,28,31undecaaza-cyclotritriacontan-2,5,8,11,14,17,20,23,26,29,32-undecaone
Autonom Name (AUN):	27-(2-dimethylamino-ethylsulfanyl)-30-ethyl-33-(1-hydroxy-2-methyl-hex-4-enyl)-6,9,18,24-tetraisobutyl-3,21-diisopropyl-1,4,7,10,12,15,19,25,28-nonamethyl-1,4,7,10,13,16,19,22,25,28,31undecaaza-cyclotritriacontan-2,5,8,11,14,17,20,23,26,29,32-undecaone
Molec. Formula (MF):	C66 H120 N12 O12 S
Molecular Weight (MW):	1305.81
Lawson Number (LN):	30809, 3125, 2817
File Segment (FS):	Stereo compound
Compound Type (CTYPE):	heterocyclic
Constitution ID (CONSID):	8102767
Tautomer ID (TAUTID):	9012490
Entry Date (DED):	2004/04/23
Update Date (DUPD):	2004/04/23



Field Availability:

Code	Name	Occurrence
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CN	Chemical Name	1
AUN	Autonomname	1
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LN	Lawson Number	3
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
DED	Entry Date	1
DUPD	Update Date	1
MP	Melting Point	1
PHARM	Pharmacological Data	2

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
RX	Reaction Documents	1
RXPRO	Substance is Reaction Product	1

All References:
ALLREF

1. Evers, Michel; Barriere, Jean-Claude; Bashiardes, Georges; Bousseau, Anne; Carry, Jean-Christophe; Dereu, Norbert; Filoche, Bruno; Henin, Yvette; Sable, Serge; Vuilhorgne, Marc; Mignani, Serge, Bioorg.Med.Chem.Lett., CODEN: BMCLE8, 13(24), <2003>, 4415 - 4420; BABS-6424663

L3 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:819403 HCAPLUS
DOCUMENT NUMBER: 132:36039
ENTRY DATE: Entered STN: 30 Dec 1999
TITLE: Preparation of cyclosporin derivatives via deprotonation reaction
INVENTOR(S): Viskov, Christian
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer SA, Fr.
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
INT. PATENT CLASSIF.:
MAIN: C07K007-64
SECONDARY: A61K038-13
CLASSIFICATION: 34-3 (Amino Acids, Peptides, and Proteins)
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9967280	A1	19991229	WO 1999-FR1480	19990621
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RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2780061	A1	19991224	FR 1998-7846	19980622
FR 2780061	B1	20010907		
AU 9942700	A1	20000110	AU 1999-42700	19990621
EP 1098903	A1	20010516	EP 1999-957167	19990621
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2002518519	T2	20020625	JP 2000-555931	19990621
US 2001025025	A1	20010927	US 2000-742008	20001222 <--

PRIORITY APPLN. INFO.: FR 1998-7846 A 19980622
WO 1999-FR1480 W 19990621

PATENT CLASSIFICATION CODES:

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9967280	ICM	C07K007-64
	ICS	A61K038-13
WO 9967280	ECLA	C07K007/64A
FR 2780061	ECLA	C07K007/64A
US 2001025025	NCL	514/009.000
	ECLA	C07K007/64A <--

OTHER SOURCE(S): CASREACT 132:36039; MARPAT 132:36039
ABSTRACT:
The invention concerns a novel method for preparing an intermediate polyanion for preparing cyclosporin derivs. by treating a cyclosporin with a hexamethyldisilazane metal salt, optionally in the presence of a metal halide. The treated cyclosporin has one or several free hydroxy groups and/or non-methylated nitrogen atoms in position α and/or any other acid group capable of deprotonation which are optionally deprotonated or in protected form. Thus, [(R)-2-(N,N-dimethylamino)ethylthio-Sar]3 cyclosporine A was prepared in 53 % yield via coupling of cyclosporine A with di-[2-(N,N-

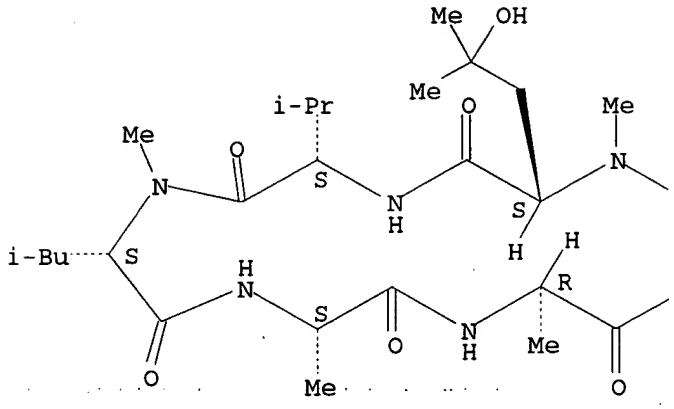
dimethylamino)ethyl] disulfide in presence of hexamethyldisilazane lithium salt and cesium chloride in tert-butylmethyl ether and toluene.

SUPPL. TERM: peptide cyclosporin prepn deprotonation coupling
INDEX TERM: Coupling reaction
Deprotonation
(preparation of cyclosporin derivs. via coupling and deprotonation reactions)
INDEX TERM: Peptides, preparation
ROLE: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of cyclosporin derivs. via coupling and deprotonation reactions)
INDEX TERM: **210758-97-7P 210759-10-7P**
227937-27-1P
ROLE: BPN (Biosynthetic preparation); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of cyclosporin derivs. via coupling and deprotonation reactions)
INDEX TERM: **624-92-0**, Dimethyl disulfide **1072-11-3**
7647-17-8, Cesium chloride, reactions
59865-13-3, Cyclosporine A **107335-26-2**
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of cyclosporin derivs. via coupling and deprotonation reactions)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD.
REFERENCE(S):
(1) Belagali, S; Indian J Chemistry 1995, V34B, P45 HCAPLUS
(2) Chu, K; J Organic Chemistry 1991, V56, P5196 HCAPLUS
(3) Rathman, T; Spec Chem 1989, V9(5), P300 HCAPLUS
(4) Sandoz AG; EP 0194972 A 1986 HCAPLUS
(5) Sandoz AG; EP 0484281 A 1992 HCAPLUS
(6) Seebach, D; Helvetica Chimica Acta 1993, V76(4), P1564 HCAPLUS
(7) Squibb & Sons Inc; EP 0379063 A 1990 HCAPLUS
(8) Wako Pure Chem Ind Ltd; EP 0357428 A 1990 HCAPLUS

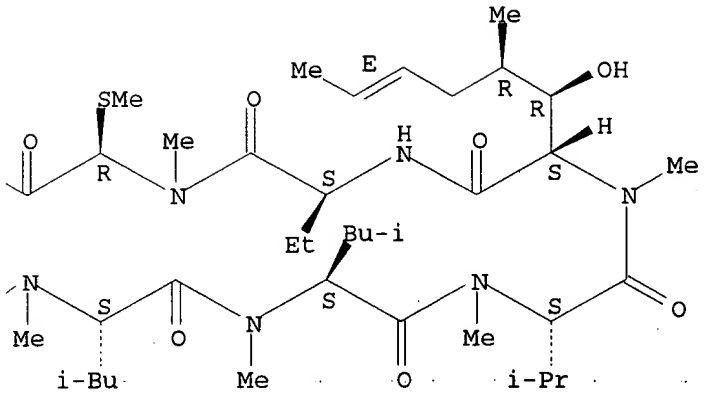
IT **210758-97-7P 210759-10-7P 227937-27-1P**
RL: BPN (Biosynthetic preparation); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of cyclosporin derivs. via coupling and deprotonation reactions)
RN 210758-97-7 HCAPLUS
CN Cyclosporin A, 8-[(2R)-N-methyl-2-(methylthio)glycine]-9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



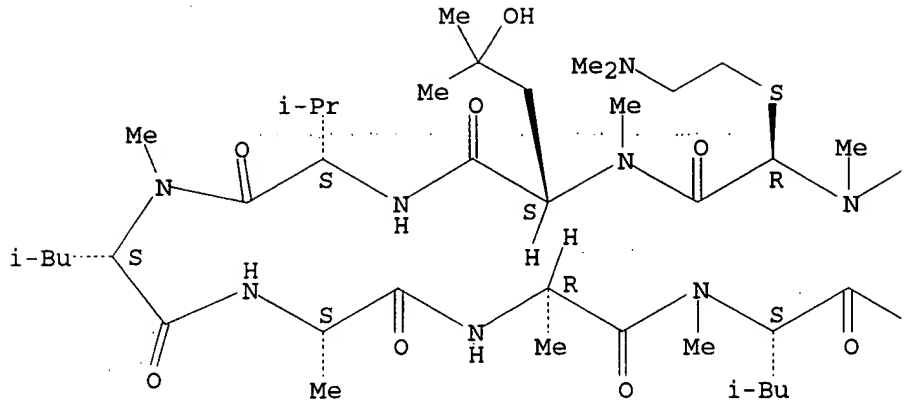
PAGE 1-B



RN 210759-10-7 HCAPLUS
CN Cyclosporin A, 8-[(2R)-2-[[2-(dimethylamino)ethyl]thio]-N-methylglycine]-9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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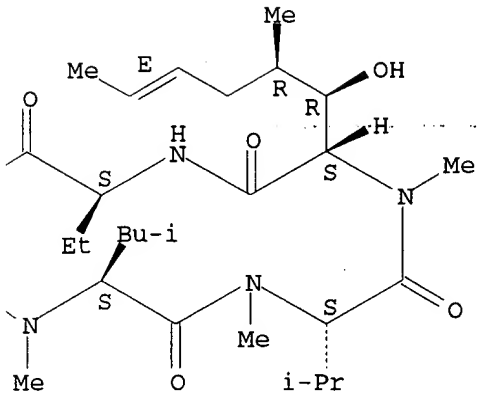


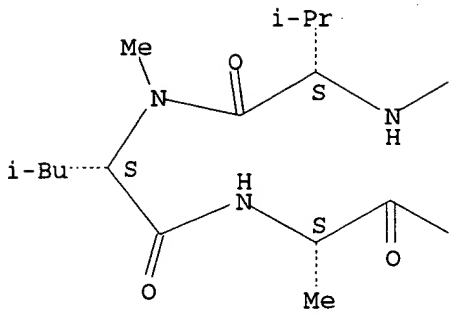
RN 227937-27-1 HCAPLUS
CN Cyclosporin A, 8-[(2R)-2-[[2-(dimethylamino)ethyl]thio]-N-methylglycine]-, monomethanesulfonate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 210760-77-3
CMF C66 H120 N12 O12 S

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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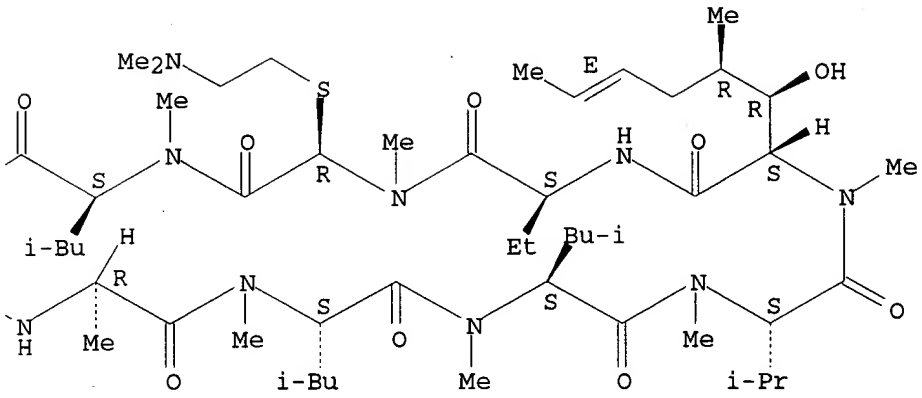
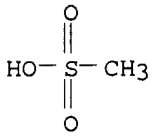


CM 2

CRN 75-75-2
CMF C H4 O3 S



IT **624-92-0**, Dimethyl disulfide **1072-11-3 7647-17-8**
, Cesium chloride, reactions **59865-13-3**, Cyclosporine A
107335-26-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of cyclosporin derivs. via coupling and deprotonation reactions)
RN 624-92-0 HCAPLUS

CN Disulfide, dimethyl (9CI) (CA INDEX NAME)

$H_3C-S-S-CH_3$

RN 1072-11-3 HCAPLUS
CN Ethanamine, 2,2'-dithiobis[N,N-dimethyl- (9CI) (CA INDEX NAME)

$Me_2N-CH_2-CH_2-S-S-CH_2-CH_2-NMe_2$

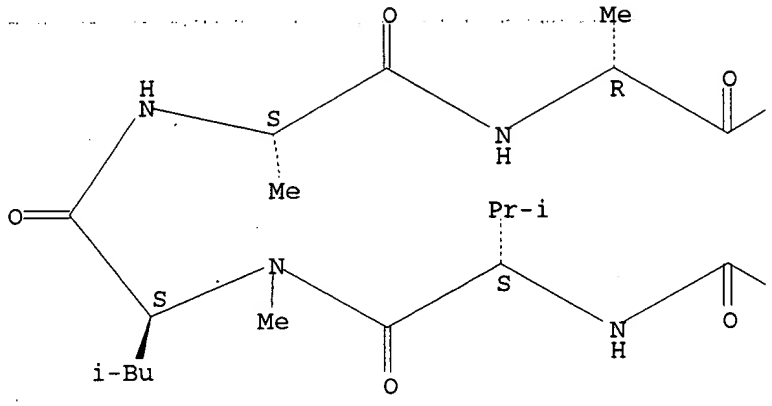
RN 7647-17-8 HCAPLUS
CN Cesium chloride (CsCl) (7CI, 8CI, 9CI) (CA INDEX NAME)

Cl—Cs

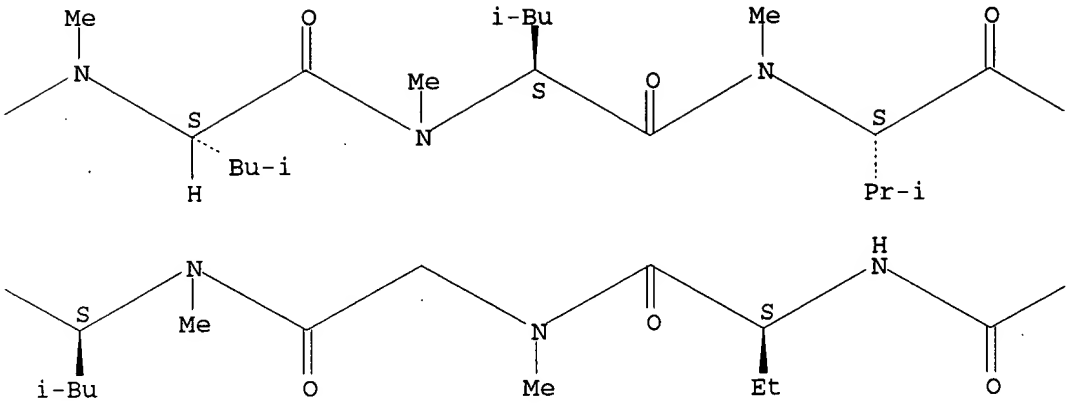
RN 59865-13-3 HCAPLUS
CN Cyclosporin A (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



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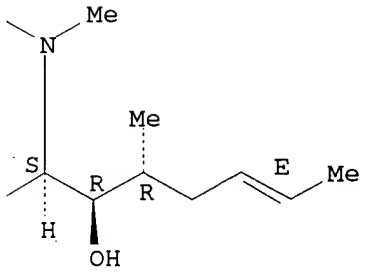
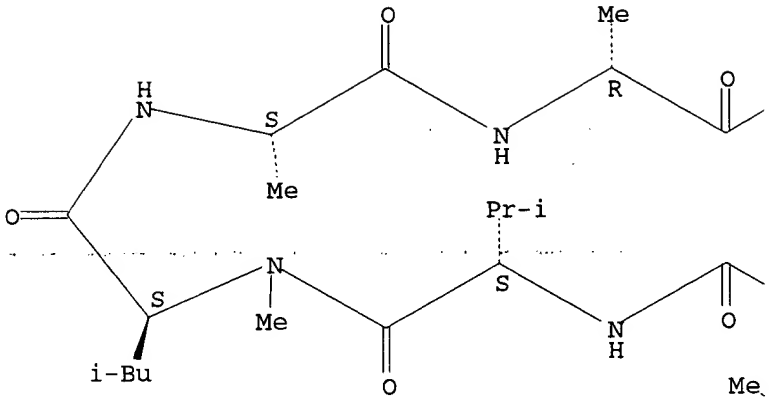


RN 107335-26-2 HCAPLUS
CN Cyclosporin A, 9-(4-hydroxy-N-methyl-L-leucine)- (9CI) (CA INDEX NAME)

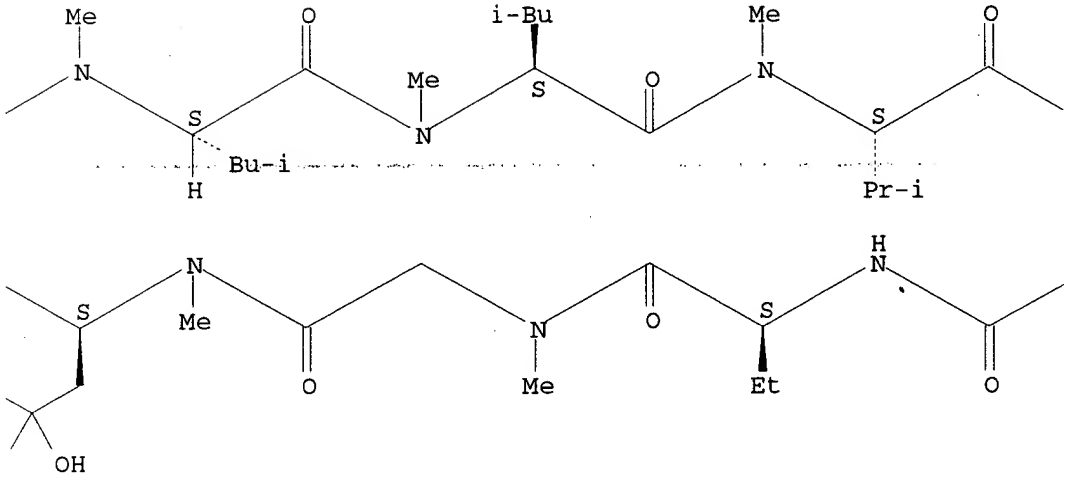
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



Me

PAGE 1-B



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